REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the remarks presented herein, which place the application into condition for allowance, or in better condition for appeal.

Status of the Claims and Formal Matters

Claims 30, 32-35, 37-47 and 49-71 are currently pending in this application. By this paper, Claim 30, 38-40, 43, 44-47, 54-56, 59 and 60-62 are amended to remove the word "about" and thus clarify the instant oral dosing, and claims 70 and 71 are added to further clarify dosing schedules.

Claim 69 was objected to under 37 C.F.R. §1.75 (c) as allegedly being in improper form because a multiple dependent claim must refer to other claims in the alternative only. By this paper, claim 69 has been amended, without prejudice, to depend in the alternative from those claims that are currently pending in this application.

As these amendments find support throughout the specification, no new matter is added.

It is respectfully submitted that the amendments presented herein are made to clarify and round out the scope of protection to which Applicants are entitled, and not for purposes of patentability within the meaning of §§101, 102, 103, or 112.

Information Disclosure Statement

Applicants respectfully submit herein as **Exhibit 1** a copy of the Information Disclosure Statement ("IDS") dated February 26, 2004 which cited references for U.S. Patent Application Serial No. 10/379,149 filed March 4, 2003. The IDS filed on April 6, 2004 regarding the instant application (10/665,079) referred to the references previously cited and produced for 10/379,149 on February 26, 2004. Applicants respectfully note that copies of these references were reviewed by the USPTO on August 7, 2006.

References cited in an Information Disclosure Statement are not required where the information was previously cited by or submitted to the Office in a prior application and this prior application is clearly identified in the Information Disclosure Statement and relied on for an earlier filing date under 35 U.S.C. §120. *See* MPEP §609(III)(A)(2). It is further noted that copies of U.S. patents and published applications are not required for all applications filed after June 30, 2003. *Id.*

Rejections under 35 U.S.C. §103(a)

Claims 30, 32-35, 37-47 and 49-69 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over DiMartino, U.S. Patent No. 6,905,669. The Office Action contends that it would have been obvious for one of skill in the art to modify the timing and dosage amounts reported in DiMartino to obtain the presently claimed methods. Applicants respectfully traverse this rejection.

Applicants urge that DiMartino relates to compositions and methods for treating diseases associated with aberrant silencing of gene expression by re-establishing the gene expression through inhibition of DNA hypomethylation and histone deacetylase. In particular, DiMartino teaches compositions comprising combinations of DNA methylation inhibitor and a histone deacetylase inhibitor (HDAC inhibitor).

Further, DiMartino teaches a laundry list of histone deacetylase inhibitors that encompass several different structural classes of compounds including hydroxamic acids and hydroxamic acid derivatives, cyclic peptides, benzamides, short-chain fatty acids, and depudecin. DiMartino describes examples of such HDAC inhibitors at col. 5, lines 43-54. DiMartino discloses dosages of the HDAC inhibitors depsipeptide, and phenylbutyrate by continuous intravenous infusion at col. 7, lines 5-31.

Notably, DiMartino fails to teach or disclose oral dosages for SAHA (or any specific dosages for SAHA whatsoever). Moreover, DiMartino fails to teach or disclose oral dosages for any HDAC inhibitor.

Under §103(a), *prima facie* obviousness is established only if 1) there is some suggestion or motivation to modify the reference or combine reference teachings, 2) there is a reasonable expectation of success, and 3) the prior art reference must teach or suggest all the claim limitations. DiMartino fails to satisfy these criteria for obviousness.

Applicants urge that one of ordinary skill in the art would not recognize how to extrapolate the generic dosages disclosed in DiMartino to apply those specifically to SAHA. Dosing for each drug must be independently established, especially here where the "genus" of HDAC inhibitors disclosed in DiMartino embraces structurally unrelated compounds. Here, the art is replete with evidence showing that SAHA is structurally different from other HDAC inhibitors like depsipeptide, and phenylbutyrate (referred to in DiMartino), and the "effective" dosing of structurally different HDAC inhibitors is markedly different. See, e.g., Figure 2 of DiMartino shows that HDAC inhibitors comprise diverse classes of compounds and have widely divergent structures.

In addition, two articles, Marks, P.A. et al, (2000) J. Natl. Cancer. Inst. 92(15): 1210-1216 ("Marks"), **Exhibit 2** and Sandor, V. et al, (2002) Clin. Cancer Res. 8: 718-728 ("Sandor"), **Exhibit 3**, enclosed herewith, provide evidence that the skilled artisan, based upon the teachings in the art, would not have the requisite reasonable expectation of success by relying upon the dosages taught by DiMartino for other HDAC inhibitors to determine the claimed dosages for oral administration of SAHA. Sandor, at page 719, col. 1, lines 8-10, expressly states that, "[d]epsipeptide, however, is structurally distinct from other known HDAC inhibitors, such as the trichostatins and trapoxins, and may have other mechanisms of cytotoxic action." Further, at page 725, Sandor teaches that "[u]nlike sodium butyrate, which has also been studied in clinical trials, depsipeptide is active in the nM range, and the induced Pgp is functional and able to transport rhodamine." This demonstrates that depsipeptide, a structurally distinct compound

from sodium butyrate and SAHA, has a significantly different potentcy. In addition, as Sandor makes clear, depsipeptide and butyrate have different mechanisms of cytotoxic action (e.g., Pgp modulation). Depsipeptide up-regulates Pgp to cause drug resistance to depsipeptide. In contrast, Applicants note that high Pgp-expressing cells are not resistant to SAHA. For these reasons, the ordinarily skilled artisan would conclude that each structurally distinct HDAC inhibitor is likely to have different dosages that depend not only on the structure of the inhibitor, but that depend on the differences in potency, specific mechanisms of action, and on differences in bioavailability.

Marks describes the plurality of structurally distinct compounds that comprise HDAC inhibitors at page 1212, under the heading, "HDAC Inhibitors". In particular, Marks teaches that "butyrates are not ideal agents because of the high concentrations required (millimolar) to achieve inhibition of HDAC activity and multiple effects on other enzyme systems." Trichostatin A, originally developed as an anti-fungal agent, inhibits HDAC at nanomolar concentrations. Oxamflatin and benzamide[1/] can inhibit HDAC activity at micromolar concentrations, while apicidin and trapoxin inhibit HDAC at nanomolar concentrations. This too would compel the conclusion in the ordinarily skilled artisan that, because of the wide range of HDAC-inhibitory concentrations among the different structural classes of HDAC inhibitors, which was known at the time the application was filed, one of skill in the art would not have a reasonable expectation of success in extrapolating a suitable or optimum dosage of SAHA from the teachings of DiMartino.

In addition, dosing must be determined independently, even for the same drug, according to the route of administration. And this was, in fact, the case for SAHA. This is well recognized -- the FDA requires a new IND for new formulations for a new route of administration. DiMartino only teaches intravenous administration of HDAC inhibitors other than SAHA. Because there is no teaching in DiMartino as to dosages of any orally-administered HDAC

1/ Applicants note that in the first human clinical trials for benzamide (aka MS-275) the initial dose (calculated on the basis of animal studies) was not predictable from preclinical

inhibitors, DiMartino fails to afford the skilled artisan with a reasonable expectation of success in arriving at the specific oral doses of SAHA claimed here. At best, DiMartino teaches that DNA methylation inhibitors can be co-administered with depsipeptide, and phenylbutyrate intravenously at the disclosed dosages, but provides no guidance as to the optimum dosages of SAHA or any of these compounds by oral administration.

It is well-known to those skilled in the pharmacological arts that different routes of administration of a particular drug will markedly affect the concentration and pharmacokinetics of different dosage forms that vary widely as a function of the compound's structure and mechanism of action. The Merck Manual of Diagnosis and Therapy provides, at Section 22, Chapter 299:

Variability In Parameter Values

Many factors affecting pharmacokinetic parameters should be considered when tailoring drug administration for a particular patient. Even with dosage adjustment, however, sufficient variability usually remains; thus, drug response and, in some cases, plasma drug concentration must be closely monitored.

Dosage: In some instances, changes in dose, dosing rate, or duration of therapy alter a drug's kinetics. For example, as dose is increased, the bioavailability of griseofulvin decreases because of the drug's low solubility in the fluids of the upper GI tract. For phenytoin, steady-state plasma concentration increases disproportionately when dosing rate is increased, because the metabolizing enzyme has a limited capacity to eliminate the drug, and the usual dosing rate approaches the maximum rate of metabolism. Plasma carbamazepine concentration decreases during long-term use because carbamazepine induces its own metabolism. Other causes of dosage-dependent kinetic changes are saturable plasma protein and tissue binding (eg, phenylbutazone), saturable secretion in the kidneys (e.g., high-dose penicillin), and saturable metabolism during the first pass through the liver (eg, propranolol).

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studies -- it was too high, and exceeded the maximum tolerated dose. See, Ryan et al., J. Clin. Oncol., 23, pp. 3912-3922 (2005) **(Exhibit 4).**

Beers, M.H., Porter, R.S., Jones, T.V. (Editors), The Merck Manual of Therapy and Diagnosis, 18th Edition, John Wiley & Sons, New York, NY (**Exhibit 5**).

Applicants previously submitted evidence that oral delivery of SAHA produced an unexpected two to three-fold increase in half life of SAHA compared to intravenous delivery. This data demonstrates that the ordinarily skilled artisan had no reasonable expectation of success in extrapolating the claimed oral SAHA doses even from SAHA IV dosing, let alone from the different IV doses in DiMartino which are only specifically exemplified for structurally unrelated HDAC inhibitors. Further, the questions that the Examiner raises regarding comparison of oral dosing of SAHA versus IV dosing (see page 5-6 of Office Action) simply highlight the conclusion that the ordinarily skilled artisan could not have any reasonable expectation of success in extrapolating IV doses from DiMartino.

As noted above, it is not simply a matter of extrapolating the dosages and expected effects of a first compound with the expectation that the dosages and pharmacologic effects would be successful for a second compound that is structurally dissimilar from the first. Based on DiMartino, the ordinarily skilled artisan could not predict with a reasonable expectation of success the oral doses of SAHA for treating diffuse large B-cell lymphomas claimed here using the IV doses of structurally unrelated HDAC inhibitors. The knowledge in the art is replete with examples that show marked differences in dosing when comparing intravenous and oral administration.

It is significant that in the present invention, SAHA is neither structurally nor pharmacologically similar to depsipeptide, and phenylbutyrate. Because of the lack of similarities, the skilled artisan cannot use the intravenous dosages of depsipeptide and phenylbutyrate taught by DiMartino and apply them to oral dosing of SAHA for treating diffuse large B-cell lymphomas as claimed here with a reasonable expectation of success. Because of this, DiMartino cannot render the claims obvious.

For the foregoing reasons, the instant application is not rendered obvious under §103(a) by DiMartino. The rejection in view of DiMartino should be withdrawn.

CONCLUSION

Favorable action on the merits is respectfully requested. If any discussion of this Amendment would be deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below and is assured of full cooperation in progressing the application to allowance.

Respectfully submitted,

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